REMARKS

The specification has been amended to correct apparent typographical and grammatical errors. It is respectfully submitted that support for the amendments may be found in the originally-filed specification, claims, and drawings. No new matter is believed to be introduced.

Claims 1-18 have been elected for prosecution in the concurrently-filed *Response To Restriction Requirement*. Claims 1-11 and 13-15 have been amended. It is respectfully submitted that support for the amendments may be found in the originally-filed specification, claims, and drawings. No new matter is believed to be introduced.

Favorable consideration of Applicants' claimed invention is respectfully solicited. No fee is believed due for this Preliminary Amendment. However, should any fee be required, please charge the required amount due to Pennie & Edmonds LLP Account No. 16-1150.

Respectfully submitted,

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EXHIBIT A

Marked Up Version Of Amended Paragraphs
U.S. Patent Application No. 09/891,715

Please amend the paragraph beginning on page 6, line 1, to read as follows:

In yet other embodiments, catheter type embodiments of the invention are able to maintain the distal end's position adjacent a target tissue during use by further including an anchor catheter. The anchor catheter is slidably situated within a third catheter having at least two lumens. The first lumen is occupied by a first catheter having an injury, treatment, and optionally marking effectors as described above, and a second lumen occupied by a second catheter having a distal end having an anchor adjacent to the second catheter distal end adapted to anchoring to an adjacent target tissue. Either the first or second catheter, or both, is capable of moving away from the other as the third catheter is withdrawn relative to both the first and second catheters, thus longitudinally exposing the first and second catheter, where then the first catheter and second catheter distal ends move away from each other a selectable distance, selected by how much a user withdraws the third catheter, and further wherein the injury and treatment effector catheter is adapted to move **circumferentially** **[circumfrentially]** about the first anchor catheter upon axial rotation of the third catheter while maintaining functional contact with the target tissue surface. In use, the third catheter is withdrawn partly as it is rotated axially. This process is continued until a spiral pattern covering the entire target area is treated.

Please amend the paragraph beginning on page 6, line 27, to read as follows:

The invention further provides for a device for treating ischemic tissue comprising an elongate shaft having proximal and distal ends, a lumen extending therebetween, a control structure operably connected to the shaft for actuation of the device by user activation, at least one injury effector adjacent the elongate shaft's distal end, and capable of inducing a mechanical or energy injury produced at a tissue site in response to actuation by the control structure**[;]** when the shaft's distal end is placed against a tissue surface, at least one therapeutic-substance delivery effector carried on the elongate shaft at the distal

end thereof, said therapeutic-substance delivery effector having at least one therapeutic-substance delivery port through which therapeutic-substance can be delivered from the effector into tissue against which the effector is placed, each of said one or more injury-treatment effectors and said one or more therapeutic-substance delivery ports being spaced from one another at selected positions and adapted to be placed simultaneously against such tissues, and[;] at least one therapeutic-substance source having a reservoir for storing a substance and in substance communication with said therapeutic-substance delivery ports, and responsive to said control structure to eject therapeutic-substance from said reservoir through said one or more ports into such tissue, wherein, said control structure, when activated by a user, operates to actuate said injury-treatment effector, and additionally actuates said therapeutic-substance source to expel therapeutic-substance through said one or more ports to create one or more sites of therapeutic-substance infusion in the tissue at defined spaced-apart locations with respect to the created one or more sites of injury.

Please amend the paragraph beginning on page 7, line 18, to read as follows:

The invention further provides for method of treating ischemic tissue. Preferred methods include methods comprising the steps of:[,]

- identifying target tissue regions of ischemic tissue,
- providing a device that can, upon activation and by a single placement of the device, cause an injury to at least one site of target tissue different than at least one site of target tissue where a therapeutic-substance is delivered,
- placing the device against the identified target tissue, and[,]
- activating the device to cause injury to selected sites within the target tissue, and to cause therapeutic-substance to be delivered to regions in the target tissue at preselected sites away from the sites of injury.

Please amend the paragraph beginning on page 7, line 30, to read as follows:

Another embodiment of the invention provides a method for treating a target tissue comprising the steps of:

- identifying the target tissue,
- producing one or more sites of injury within said region, where multiple sites of injury, if produced, are at known relative positions with respect to one another, and
- infusing therapeutic-substance into **one [on]** or more sites different than the one or more sites of injury.

Please amend the paragraph beginning on page 8, line 6, to read as follows:

Another embodiment provides a method for treating ischemic tissue comprising the steps of:

- identifying a region of ischemic tissue within a patient's body,
- producing one or more sites of injury within such region, where multiple sites, if produced, are at known relative positions with respect to one another, and
- infusing therapeutic-substance into one or more sites different from such injury sites and at known positions away from such injury sites.

Please amend the paragraph beginning on page 10, line 3, to read as follows:

Figure 2 depicts a close-up view of elongate shaft's 102 distal end 106. Here, injury effector 110 is surrounded by therapeutic-substance delivery effectors 108**, the injury effector 110 and therapeutic-substance delivery effectors 108 being [and are]** shown in their extended position protruding out from the distal end 106.

Please amend the paragraph beginning on page 10, line 7, to read as follows:

Figure 3 depicts a cross-sectional view of distal end 106 having radially distributed therapeutic-substance delivery effectors 108 distributed about centrally located injury effector 110. Cap 130 closes **off [of]** lumen 126 created by distal end 106. Injury effector 110 passes through lumen 126 and is electrically isolated from lumen 126 where electrical energy is used as an injury energy. Distal end input port 128 is in substance communication with lumen 126 and adjacent therapeutic-substance delivery effectors 108 and therapeutic-

substance delivery ports 108a and is in substance communication with a therapeutic-substance reservoir, not shown.

Please amend the paragraph beginning on page 12, line 11, to read as follows:

Figures 11a-1 through 11d-2 depict**[s]** effector arrangements and corresponding results. Figures 11a-1 through 11d-1 depict cross-sectional arrangements of single injury effectors located among a plurality of therapeutic-substance delivery effectors. Figures 11a-2 through 11d-2 depict the resulting pattern of treatments in target tissue from corresponding arrangements applied in a linear fashion. Figure 11 further depicts the result produced by methods provided by the present invention. The invention provides a method for treating a target tissue comprising the steps of first identifying the target tissue, then producing one or more sites of injury within said region, where multiple sites of injury, if produced, are at known relative positions with respect to one another, and infusing therapeutic-substance into **one** **[on]** or more sites different than the one or more sites of injury. Another embodiment provides a method for treating ischemic tissue comprising the steps of first identifying a region of ischemic tissue within a patient's body, and then producing one or more sites of injury within such region, where multiple sites, if produced, are at known relative positions with respect to one another, and infusing therapeutic-substance into one or more sites different from such injury sites and at known positions away from such injury sites.

Please amend the paragraph beginning on page 13, line 3, to read as follows:

The present invention provides methods and devices for stimulating angiogenesis in or near ischemic heart tissue, and for stimulating regeneration of tissue. The invention provides a combination of two, or optionally three, different treatments with the single placement of one device against a tissue targeted for enhanced vascularization. Treatments are applied through separate treatment effectors. The first treatment creates a site of injury. The second treatment infuses a substance, for example, therapeutic-substance compounds or cells, into a position selected away from the injury site at pre-selected and fixed locations away from the first injury site. The third, optional, treatment creates a position marker site

so that a user may later identify tissue regions previously treated by the device of the present invention. Each treatment may occur in sequential order in any combination, or simultaneously, or may occur as a combination of sequential and simultaneous events. After all of the events occur, the treated area then has one or more sites of injury caused by the first treatment. The injury site or sites are surrounded, in whole or in part, by regions of therapeutic-substance, delivered during the second treatment. And, optionally, at least one position market **is** located within or adjacent to either the resulting site of injury, or the therapeutic-substance delivery site, or a third site or set of sites distinct from the injury and therapeutic-substance sites. Other embodiments of the present invention provide for therapeutic-substance delivery sites surrounded by one or more injury sites.

Please amend the paragraph beginning on page 13, line 23, to read as follows:

In use, the device is typically placed inside a patient by urging the device's distal end toward a region of a patient's heart earlier determined to be ischemic or otherwise amenable to the treatment provided by the present invention. The patient's heart is made accessible to the device by open surgery, thoroscopic portals, or intravascularly by inserting a catheter form of the present invention into the body and navigating its distal end toward the area within the patient's body that is sought to be treated. Once positioned near the area of the tissue to be treated, also known as the target tissue, the distal end of the device is manipulated such that the device's thrust axis is perpendicular to the surface of the target tissue. Incorporation of a perpendicularity sensing device, for example, a force contact transducer, as described in U.S. Provisional Patent Application No. 06/191,610 by Tom, filed March 23, 2000, or ultrasonic transducer described by Zannelli in U.S. Patent No. 6,024,703, both **of** which are entirely incorporated by reference herein, can aid a user in attaining a perpendicular relation between the thrust axis of the tool and the target tissue surface so that tissue penetration by the device is substantially perpendicular to the target tissue surface.

Please amend the paragraph beginning on page 16, line 4, to read as follows:

Therapeutic-substance delivery may **be** augmented by the application of gentle electrical current to the second treatment needles thus urging the therapeutic-substance into tissue adjacent such second treatment needles by iontophoresis or other electromotive force. Again, a circuit is created between such electrode second treatment needles and a point in the patient distal to the site of the second treatment needle, for example, a remote "grounding pad" or, alternatively, the first treatment needle, or both in combination or opposition (asynchronous).

Please amend the paragraph beginning on page 16, line 11, to read as follows:

The third treatment may optionally be applied to the target tissue through the first treatment needle, the second treatment needle, or a third treatment needle, or any combination of the three. The third treatment aims to provide some indication that a region has been visited by the device resulting in treatment. Such indication permits the user to thoroughly cover an area of target tissue sites without either omitting or repeating application to a particular site. The present invention provides for either simultaneous or independent activation of the position marker. Moreover, the ability to use needles from the first, **[or]** second, **or** both treatments simplifies the architecture of the device. Another benefit is the ability to inject position marking compounds, for example, contrast agents and fluoroscopic or radio-opaque dyes into the target tissue at a location different than the site of injury, or the site of therapeutic-substance delivery. This feature is beneficial when such marking compounds may interfere with other functions or objectives of the device such as interfering with the therapeutic-substance activity. Injecting marking compounds also widens the array of choices for suitable marking compounds. Contrast agents and radio-opaque dyes, for example, may not be suitable for a stamping method because such agents and dyes may simply wash off the tissue surface without leaving a discernable mark. Injecting such agents and dyes helps to localize such agents and dyes for longer time periods. Alternatively, marking may also occur as a side effect of the first treatment, for example, as when a laser beam is used to cause tissue injury thus leaving a visually perceptible mark. The present invention further provides for position marking, the third

treatment, to be done either simultaneously or independent from the actuation of the injury or first treatment, and the therapeutic-substance delivery or second treatment. Independent actuation of the third treatment affords the user the ability to mark off a region with boundaries, for example, by radio-opaque dye, without applying the first and second treatments to such marking areas. The user may then switch to a simultaneous mode to fill in the now defined region with all three treatments thus leaving a position mark at each treatment location between the earlier made boundary marks. Other embodiments of the invention use a stamp to "tattoo" a treatment area with a dye, for example, methylene blue. Fluorescent dyes may also be used and their emission wavelength visualized when the dye is excited.

Please amend the paragraph beginning on page 18, line 10, to read as follows:

In preferred embodiments, effectors are combined in an effector structure. The effector structure serves to maintain the position of effectors as they are urged into a target tissue. The effector structure may also aid in establishing substance communication between the therapeutic-substance reservoir and each effector. The effector structure may also act as a manifold, as discussed above. In preferred embodiments, the effector is in mechanical communication with a force applicator, operably connected to an actuator so that when the actuator is actuated by the user, the force applicator will apply force to the effector structure to urge at least one treatment, and preferably two or more **[treatment]** different treatment effector or effectors toward the target tissue such that those effectors are urged or otherwise advanced into the target tissue. Other embodiments provide for separate force applicators for each type of treatment effector, for example a first force applicator which applies force to a first treatment effector, and a second force applicator which applies force to a second force applicator. Such several force applicators may operate in unison, or individually, or both where the user may select each mode of operation. Force applicators, in conjunction with their respective effector structures and treatment effectors, may further operate in unison, or separately, or both from a therapeutic-substance delivery actuator which causes the therapeutic-substance reservoir to deliver therapeutic-substance via the above described conduits and treatment effectors.

Please amend the paragraph beginning on page 19, line 14, to read as follows:

The control structure, in preferred embodiments, includes a single control for actuating the treatment effectors in a preset manner dictated by the device's configuration, and causing the delivery of therapeutic-substance or therapeutic-substances from at least one therapeutic-substance reservoir. Other embodiments provide for separate controls actuating separately different treatment effectors, and separately, or in tandem with a particular type of treatment effector, actuating a therapeutic-substance reservoir. Yet other embodiments provide for combinations of the above described controls. Controls may further be integrated with other components of the device such as the above described force contact transducer to provide an interlock between the force applicator or applicators and their respective controls. The force contact transducer would permit activation of a force applicator, hence a treatment effector, only if the proper axial force or thrust was applied to the tool in the direction of the target tissue and that the trust axis was essentially perpendicular to the target tissue.

Please amend the paragraph beginning on page 19, line 28, to read as follows:

Although the invention has been described with reference to a particular embodiment, it will be appreciated that various **[and]** changes and modifications may be made without departing from the spirit of the invention.

EXHIBIT B

Marked Up Version Of Amended Elected Claims
U.S. Patent Application No. 09/891,715

1. (Amended) A device for treating ischemic tissue**, the device** comprising**:**

an elongate shaft having proximal and distal ends, a lumen extending therebetween;

a control structure operably connected to the shaft for actuation of the device by user activation;

at least one injury effector adjacent the elongate shaft's distal end, and capable of inducing a mechanical**, chemical, substance,** or energy injury produced at a tissue site in response to actuation by the control structure**[;]** when the shaft's distal end is placed against **or near** a tissue surface;

at least one therapeutic-substance delivery effector carried on the elongate shaft at the distal end thereof, said therapeutic-substance delivery effector having at least one therapeutic-substance delivery port through which therapeutic-substance can be delivered from the **therapeutic-substance delivery** effector into tissue against **or near** which the **therapeutic-substance delivery** effector is placed, each of said one or more injury**[-treatment]** effectors and said one or more therapeutic-substance delivery ports being spaced from one another at selected positions and adapted to be placed simultaneously against **or near** such tissue**[s]**; and

at least one therapeutic-substance source having a reservoir for storing a substance and in substance communication with said **one or more** therapeutic-substance delivery ports, and responsive to said control structure to eject therapeutic-substance from said reservoir through said one or more **therapeutic-substance delivery** ports into such tissue**;[,]**

wherein, said control structure, when activated by a user, operates to actuate **at least one of said one or more [said]** injury**[-treatment]** effector**s**, and additionally actuates said therapeutic-substance source to expel therapeutic-substance through said one or more **therapeutic-substance delivery** ports to create one or more sites of therapeutic-substance

infusion in the tissue at **one or more** defined spaced-apart locations with respect to the created one or more sites of injury.

2. (Amended) The device of claim 1 further comprising a **marking [third treatment]** effector for creating a treatment position marker.

3. (Amended) The device of claim 2 wherein the **marking [third treatment]** effector is separate from the injury and therapeutic-substance delivery effectors.

4. (Amended) The device of claim 2 wherein the marking effector is combined with **at least one of [either]** the injury**[,]** or therapeutic-substance delivery **effectors.[, or injury and therapeutic-substance delivery effector.]**

5. (Amended) The device of claim 1 wherein **at least one of** the **one or more** injury **effectors** and **at least one of the one or more** therapeutic-substance delivery effectors actuate simultaneously.

6. (Amended) The device of claim 1 wherein **at least one of** the **one or more** injury **effectors** and **at least one of the one or more** therapeutic-substance delivery effectors actuate sequentially.

7. (Amended) The device of claims 2, 3, or 4 wherein **at least one of** the **one or more** injury **effectors, at least one of the one or more** therapeutic-substance delivery **effectors**, and **the [position-]**marking effector**[s]** actuate simultaneously.

8. (Amended) The device of claims 2, 3, or 4 wherein **at least one of** the **one or more** injury **effectors**, **at least one of the one or more** therapeutic-substance delivery **effectors**, and **the [position-]**marking effector**[s]** actuate sequentially.

9. (Amended) The device of claims 2, 3, or 4 wherein the **[position-]**marking effector actuates independently from the **one or more** injury effectors or **the one or more** therapeutic-substance delivery effectors.

10. (Amended) The device of claim 1 wherein the therapeutic-substance**[-]**source is actuated independent of the actuation of **at least one of the one or more [the]** therapeutic-substance delivery effectors.

11. (Amended) The device of claim 1 wherein the therapeutic-substance**[-]**source is actuated simultaneous to the actuation of **at least one of the one or more [the]** therapeutic-substance delivery effectors.

13. (Amended) The device of claim 1 further comprising an optical viewing port located at **or proximate** the elongate shaft's distal end **and being** in optical communication with an imaging device.

14. (Amended) The device of claim 1 wherein the elongate shaft further comprises a contact sensor located **at or proximate [on]** the elongate shaft's distal end.

15. (Amended) The device of claim 1 wherein the elongate shaft further comprises a positioning aid located **at or proximate [on]** the elongate shaft's distal end.